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The History of Diagnosing Venous Thromboembolism

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Abstract

An accurate and prompt diagnosis of deep vein thrombosis and/or pulmonary embolism is important to prevent serious complications and mortality. Because the clinical presentation of venous thromboembolism (VTE) is often nonspecific, objective testing by means of radiological imaging is required to confirm the diagnosis. Historically, a diagnosis of VTE involved invasive imaging techniques like contrast venography or conventional pulmonary angiography. Technological developments toward more accurate and less invasive diagnostics have driven the implementation of a variety of newer technologies over the past decades, as well as the derivation and validation of clinical decision rules (CDRs) that can be used to rule out VTE in combination with D-dimer blood tests. In this narrative review, we provide a historical overview of the most notable developments in the imaging techniques and CDRs for VTE diagnosis.

Keywords

- venous thromboembolism
- deep vein thrombosis
- pulmonary embolism
- radiology
- diagnosis
- algorithm
- historical

Over the past decades, important advances have been made in the diagnostic management of venous thromboembolism (VTE). In this narrative review we provide a historical overview of the developments in the imaging techniques (►**Fig. 1**) and clinical decision rules (CDRs) for VTE diagnosis.

Evolution in Imaging Techniques to Diagnose Deep Vein Thrombosis of the Lower Extremity

One of the earliest diagnostic imaging techniques for studying the deep veins is contrast venography (also called phlebography or functional ascending phlebography). Its first reported use in human patients was in 1923 by Berberich and Hirsch, who injected an aqueous solution of strontium bromide into the vein of the arm.[1] After a brief period, contrast venography lost its popularity for a while, mainly due to faulty techniques (e.g., horizontal position of extremity, improper contrast material, or injection site) that caused diagnostic misclassification and nondiagnostic (i.e., inconclusive) test results.[2] In the absence of a safe and reliable imaging test, the diagnosis of deep vein thrombosis (DVT) was mostly established on clinical grounds until the 1960s. However, after many years of improvements in the application and interpretation of contrast venography, it became evident that signs and symptoms were inaccurate for diagnosing DVT and improved venography techniques were considered the diagnostic standard from then on.[3] A review from 1943 evaluated the diagnostic accuracy of clinical gestalt versus contrast venography, in patients receiving contrast venography as a standard procedure prior to femoral vein ligation to provide more clearly defined indications for the surgical procedure. The authors found that clinical gestalt had a sensitivity of 74% and a specificity of 50%. Despite clinical signs of DVT, 21% of patients ($n = 27$) had negative venography results, whereas 15% patients ($n = 19$) with no clinical signs of DVT had positive venography results.[4] Although the method of contrast venography had been improved considerably, the procedure continued to have disadvantages: it is invasive, often painful, relatively

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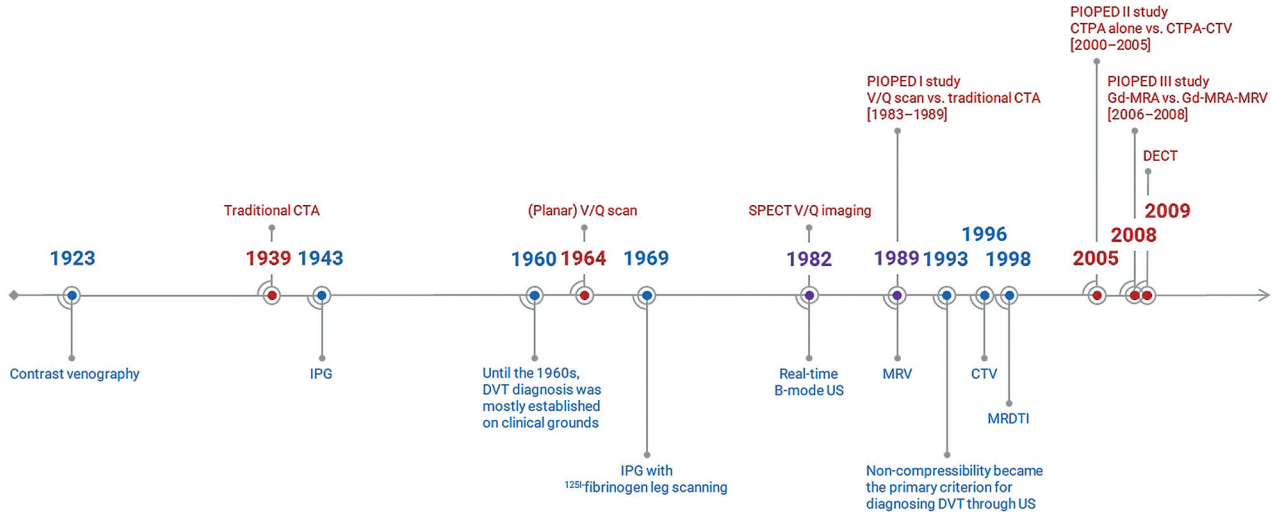


Fig. 1 Timeline of advancements in diagnostic imaging modalities for venous thromboembolism. Imaging modalities used to diagnose deep vein thrombosis are represented in blue, while those for diagnosing pulmonary embolism are depicted in red. CTA, computed tomography angiography; CTPA, computed tomography pulmonary angiography; CTV, computed tomography venography; DECT, dual-energy computed tomography; DVT, deep vein thrombosis; IPG, impedance plethysmography; MRDTI, magnetic resonance direct thrombus imaging; MRV, magnetic resonance venography; PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis; SPECT, single-photon emission computed tomography ventilation/perfusion; US, ultrasound; V/Q scan, ventilation/perfusion scan.

expensive, and requires considerable skill and experience of the operator. Consequently, many attempts have been made to develop reliable, noninvasive imaging modalities.

In the 1940s, impedance plethysmography (IPG) was introduced as a noninvasive alternative technique to venography in the diagnostic management of patients clinically suspected of acute DVT.[5] The underlying principle of this simple diagnostic test for the diagnosis of DVT concerns changes in electrical resistance or impedance resulting from diminished venous return, due to intravascular thrombotic obstruction. Compared with venography, the technique was found to be sensitive and specific in patients with symptomatic proximal DVT of the lower limbs (popliteal, femoral, or iliac veins), but relatively insensitive to isolated calf vein thrombosis, as well as to nonobstructing proximal DVT.[6] As a result, for a considerable time, IPG was used in combination with ^{125}I fibrinogen leg scanning. The latter technique uses radioiodine-labeled fibrinogen to detect freshly developing or extending thrombi and was considered to be particularly sensitive to subclinical leg DVT. Although several studies found the combined approach of IPG and ^{125}I fibrinogen leg scanning to be sensitive and specific for both proximal-DVT and calf-DVT, new insights into the natural history of DVT placed the significance of isolated calf-DVT detection and treatment, and thus ^{125}I fibrinogen leg scanning, into a different perspective.[7] In 1981, it was stipulated that a person's embolic risk is determined by location of DVT; isolated calf-DVT would pose a low risk of acute pulmonary embolism (PE) compared with proximal DVT.[8] In addition to this, Philbrick stated that there was no convincing evidence that DVT confined to the calf would lead to chronic venous insufficiency and that the risks associated with anticoagulation would exceed the risk of withholding anticoagulant treatment in this setting.[9]

In the early 1980s there was a major breakthrough in venous clot detection. The technologist Talbot discovered that one could easily visualize differences between normal veins and veins that contained clots using a combination of pulsed Doppler and real-time B-mode ultrasonography (US).[10] B-mode US displays the intensity of returning echoes as varying shades of gray or color, permitting a two-dimensional cross-sectional representation of the veins. He noted that when a vein was obstructed, the vein diameter would not alter with respiration (Valsalva maneuver) or light pressure applied to the skin surface (►**Figs. 2** and **3**). Moreover, obstructed veins often contained a speckled mass and tended to be enlarged. Since Talbot's successful discovery, additional studies supported the use of venous US. Consequently, the use of venography waned, as US gradually emerged as the modality of choice for the diagnosis of acute thrombosis of the lower limbs. While different diagnostic criteria have been proposed to be useful for distinguishing normal from abnormal veins, (non)compressibility of the vein was considered the most important criterion.[11,12] A group from New York University, led by Raghavendra, noted that venous distention during Valsalva's maneuver was unreliable as criterion because of susceptibility to interpretation errors.[12] In addition, a sonographic detection of a speckled mass in the lumen of the vein appeared challenging in the case of fresh thrombi, as they are acoustically only slightly denser than flowing blood and thus appear (almost) anechoic. For the aforementioned reasons, nowadays, all different US techniques still rely in some degree on compression.[13] A prospective study from 1989 demonstrated that using noncompressibility as the sole criterion for the detection of proximal DVT in 220 symptomatic outpatients, real-time B-mode US is highly accurate, simple, objective, and reproducible.[11] When compared with the standard contrast venography, US yielded a sensitivity of 100% (95% confidence interval [CI], 95–100) and specificity of 99% (95% CI, 97–100). The interobserver agreement for the independent assessment of each sonogram was 100%.

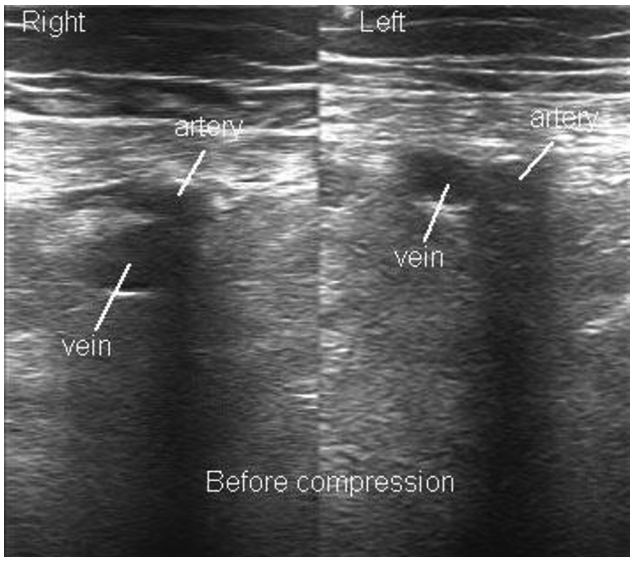


Fig. 2 Ultrasonographic image of femoral vessels without compression. Reproduced with permission Grimm and Manson 2021.[89]

In response to the increasing use of computed tomography pulmonary angiography (CTPA) for patients suspected of having acute PE in the late 1990s, many investigators advocated the routine use of CT venous phase imaging (CTV) as an adjunct to CTPA to detect concomitant DVT of the pelvis or the lower extremities.[14] While CTV and compression ultrasonography (CUS) provide similar diagnostic accuracy for nonpelvic vein thrombosis, CTV combined with CTPA greatly simplified the diagnostic workup because a separate examination of the lower extremities was no longer required. Using the contrast material already in the circulation after CTPA, CTV allows indirect imaging of thrombi in the abdominopelvic or lower extremity veins, adding only a few minutes to the overall examination. Several studies showed an increase in the detection rate of VTE by CTV combined with CTPA compared with the single CTPA examination.[15,16] However, the absolute gain owing to CTV appeared to be limited to the overall diagnosis of VTE during 3-month follow-up.[17] With the disadvantage of more ionizing radiation and the potential for overdiagnosis and overtreatment of patients due to false-positive test results, the current literature argues against routine use of CTV. Nonetheless, the technique can be beneficial for a subset of patients, such as those patients with suspected DVT extending into the inferior vena cava.

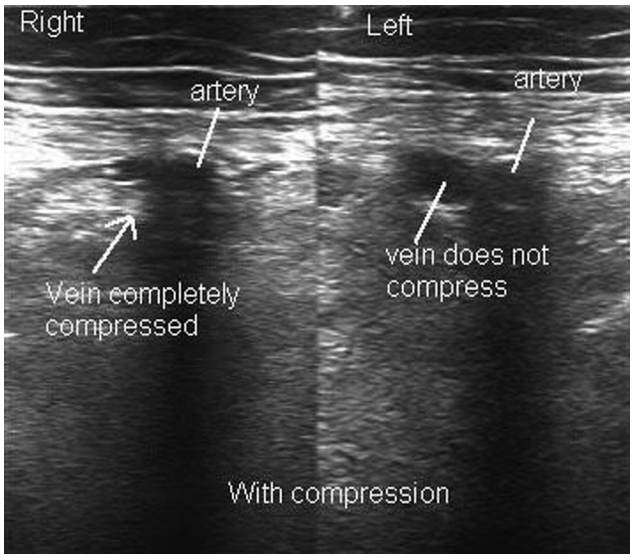


Fig. 3 Ultrasonographic image of femoral vessels with compression. Noncompressibility (thrombosis) in the left common femoral vein. Reproduced with permission Grimm and Manson 2021.[89]

In the same period, magnetic resonance venography (MRV) had evolved as an established and valuable tool in the diagnosis of DVT in specific patient populations.[18] MRV offers advantages, such as noninvasiveness, quicker acquisition times, and the absence of ionizing radiation. With pelvic radiation being a major concern in CTV, especially in young patients with highly radiosensitive reproductive organs, and considering the limitations of CUS in the pelvic region, MRV overcomes the disadvantages of these imaging modalities.

In 1998, Moody et al introduced a contrast-free magnetic resonance imaging (MRI) technique called magnetic resonance direct thrombus imaging (MRDTI).[19] Many issues associated with conventional techniques (e.g., radiation exposure, interobserver variability, (inability of) venous cannulation, limited visualization in the pelvic region, and persistent intravascular abnormalities) were overcome with this novel technique that directly visualizes thrombus. The underlying concept involves the transformation of hemoglobin into methemoglobin within a fresh thrombus. This substance serves as an endogenous contrast agent, appearing with a high-signal intensity on a T1-weighted MRI sequence.[20–23] With the high signal persisting for up to 6 months, the technique has the ability to distinguish between acute and chronic thrombi. Despite its promising role in the diagnostic management of DVT, higher costs and restricted availability prohibited MRDTI from becoming a first-line diagnostic imaging test.

At present, CUS, combined or not with color Doppler, is the first-line imaging technique for the diagnosis of DVT in daily clinical practice, whereas MRDTI can be used as a second-line test for patients in whom CUS is inconclusive.[24,25] Furthermore, MRDTI has also been suggested as primary test for the diagnostic management of patients suspected of having acute, recurrent, ipsilateral, proximal DVT of the leg following the promising results from a prospective diagnostic outcome study (►**Fig. 4**).[26–29] The study showed a low 3-month incidence of VTE recurrence after negative MRDTI in patients clinically suspected of having acute recurrent ipsilateral DVT of the leg. The failure rate among patients with a negative MRDTI result for DVT at baseline and who did not receive anticoagulant treatment during follow-up was 1.7% (95% CI, 0.2–5.9). Moreover, MRDTI proved to be a feasible and reproducible diagnostic test across different international academic and nonacademic study sites. Finally, upcoming data from the Tethys study on the diagnostic performance of MRDTI in pregnant patients are expected in the near future, potentially bringing clarity to the clinical dilemma of detecting pelvic vein thrombosis in this clinical setting (NTR code: NL7498).[30]

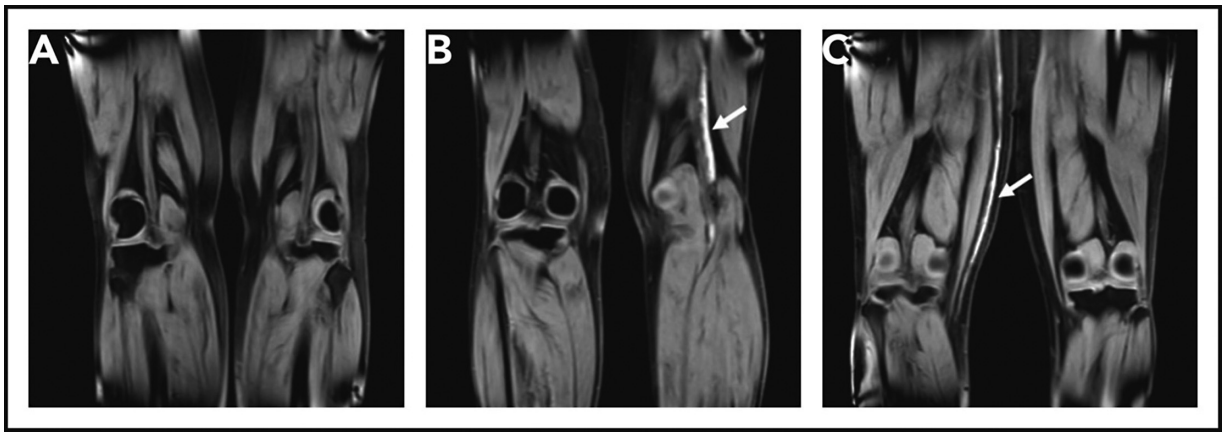


Fig. 4 Coronal MRDTI images from three study patients of a prospective diagnostic outcome study. (**A**) MRDTI negative for DVT with symmetric low signal intensity in both popliteal veins, despite an incompressible popliteal vein in the left leg upon CUS. (**B**) Asymmetrical high-signal intensity in the left popliteal vein diagnostic of acute recurrent DVT of the left leg (arrow). (**C**) Asymmetrical high-signal intensity in the right great saphenous vein diagnostic for acute thrombophlebitis, but not DVT, in the right leg (arrow). CUS, compression ultrasonography; DVT, deep vein thrombosis; MRDTI, magnetic resonance direct thrombus imaging. Reproduced with permission: van Dam et al 2020.[26]

Finally, various other imaging modalities such as 99mTc-recombinant tissue plasminogen activator scintigraphy imaging, ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography (^{18}F-FDG PET/CT), and US elastography have been developed for detecting acute thrombosis or to differentiate acute thrombosis from chronic thrombosis.[31–33] However, these radiological techniques have only been studied to a limited extent and have not found their way into clinical practice.

Evolution in Imaging Techniques for Pulmonary Embolism

PE is a potentially fatal disease that warrants early detection and treatment.[34] Delayed diagnosis or misdiagnosis is nonetheless common.[35] It has been long recognized that PE is notoriously difficult to diagnose as the clinical signs and symptoms of acute PE lack diagnostic accuracy, being neither sensitive nor specific to diagnose or exclude this condition.[36–38] The diagnosis of PE therefore relies on additional tests, including imaging techniques.

For many years, pulmonary angiography involving invasive right heart catheterization was the only imaging technique available for the diagnosis of acute PE. This technique was originally described in 1939 by Robb and Steinberg, pioneers in cardiovascular imaging by using intravenous contrast injection.[39] Due to the invasive nature of the test and the procedure-related mortality, this gold standard technique was replaced by the (planar) ventilation–perfusion radionuclide scan, also called V/Q scan, or ventilation/perfusion scintigraphy. Its initial use was reported in 1964 by Quin et al.[40] V/Q-imaging allows an indirect diagnosis of PE, a so-called mismatched defect (i.e., reduced or absent perfusion in areas of the lung that are usually ventilated) representing PE, since perfusion is absent or reduced but ventilation is still normal. Since mismatched defects can also be seen in other settings, several diagnostic criteria have been proposed for the optimal and standardized interpretation of these radionuclide scans, of which Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) and the modified PIOPED are most well-known.[41,42] The landmark PIOPED study, conducted between 1983 and 1989, compared the diagnostic accuracy of V/Q scans, using the so-called PIOPED criteria (►**Table 1**), against the traditional pulmonary angiography for the diagnosis of PE in 1,493 patients suspected of having PE.[42] One of the main weaknesses of the PIOPED criteria was that the majority of the patients (73%) had an intermediate- or low-probability V/Q scan category, leaving clinicians with a high proportion of inconclusive or nondiagnostic results. Moreover, compared with the other scan categories and angiogram readings, the interobserver agreement was considerably lower in the intermediate- and low-probability V/Q scan categories. Consequently, the PIOPED criteria were revised (►**Table 2**) in 1993 by Gottschalk et al following retrospective analyses of the original PIOPED data.[41,42] The main changes encompassed the recategorization of single segmental mismatched perfusion defects into the intermediate, rather than the conventional low-probability category and the incorporation of a "very low-probability" category for several specific abnormalities, which were identified to correspond to a PE likelihood of less than 10%. These modified criteria were prospectively validated in the multicenter PIOPED II study between 2000 and 2005.[43] This study investigated the diagnostic accuracy of contrast-enhanced multidetector CTPA alone, as well as combined with CTV of the pelvic and lower extremity veins using a composite reference test (i.e., V/Q scan, CUS of the lower extremities, and if necessary, pulmonary digital subtraction angiography) to confirm or rule out PE. The study showed that multidetector CTPA combined with CTV had a higher sensitivity (90%) than CTPA alone (83%), whereas the specificity was similar with specificities of 95 and 96%, respectively. However, combined CTPA–CTV had a higher proportion of inconclusive imaging investigations compared with CTPA alone, owing to poor image quality of either CTPA or CTV (11 vs. 6%). Including these inconclusive investigations would have resulted in a lower sensitivity for both CTPA and CTPA–CTV.

Table 1 PIOPED scan interpretation categories and criteria

Scan interpretation categories[a]	Scan interpretation criteria
Normal	• No perfusion defects present • Perfusion outlines exactly the shape of the lungs as seen on the chest X-ray (hilar and aortic impressions may be seen, chest X-ray and/or ventilation study may be abnormal)
Very low probability	• ≤3 small segmental perfusion defects with a normal chest X-ray
Low probability	• Nonsegmental perfusion defects (e.g., cardiomegaly, enlarged aorta, enlarged hila, elevated diaphragm) • Single moderate mismatched segmental perfusion defect with normal chest X-ray • Any perfusion defect with a substantially larger chest X-ray abnormality • Large or moderate segmental perfusion defects involving no more than four segments in one lung and no more than three segments in one lung region with matching ventilation defects either equal to or larger in size and chest X-ray either normal or with abnormalities substantially smaller than perfusion defects • > 3 small segmental perfusion defects (<25% of a segment) with a normal chest X-ray
Indeterminate or intermediate probability	• Not falling into normal, very-low-, low-, or high-probability categories • Borderline high or borderline low • Difficult to categorize as low or high
High probability	• ≥2 large (>75% of a segment) segmental perfusion defects without corresponding ventilation or X-ray abnormalities or substantially larger than either matching ventilation or chest X-ray abnormalities • ≥2 moderate segmental (≥25 and ≤75% of a segment) perfusion defects without matching ventilation or chest X-ray abnormalities and one large mismatched segmental defect • ≥4 moderate segmental perfusion defect without ventilation or chest X-ray abnormalities

Abbreviations: PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis; V/Q, ventilation/perfusion scan.
Source: PIOPED Investigators 1990.[42]
Notes: Scan readings were adjudicated as near normal/normal probability if the scans were classified as very low probability by one reader and low probability by the other, very low probability by both readers, very low probability by one reader and normal by the other, and normal by both readers.
[a]The final adjudicated V/Q scan readings consisted of four categories: high probability, intermediate probability (indeterminate), low probability, and near normal/normal probability.

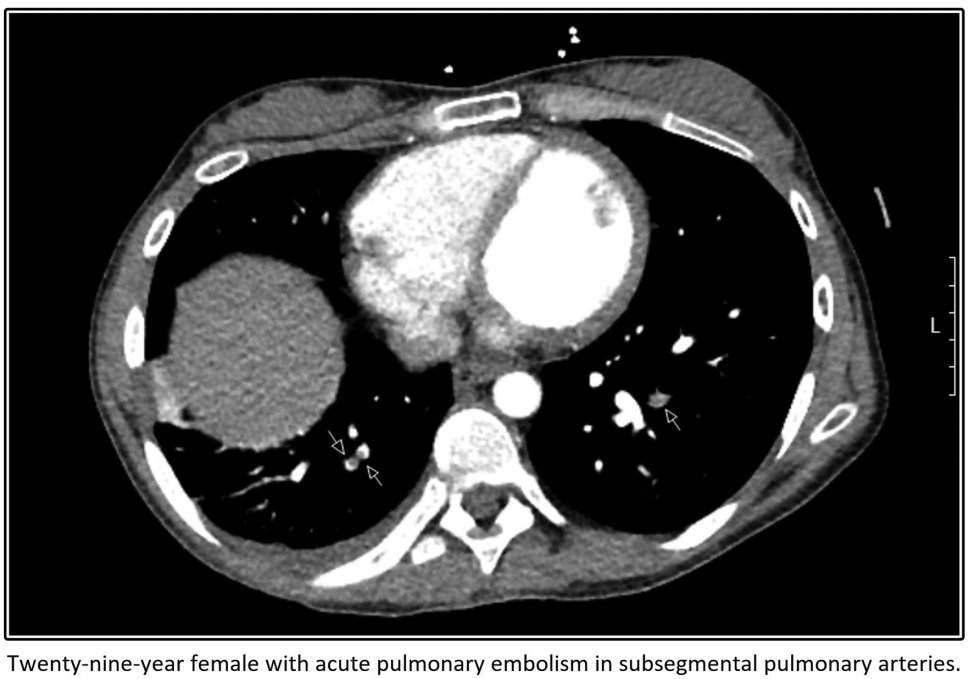
Table 2 The modified PIOPED (II) scan interpretation categories and criteria

Scan interpretation categories	Scan interpretation criteria
Normal	• No perfusion defects • Perfusion outlines exactly the shape of the lungs as seen on the chest X-ray (hilar and aortic impressions may be seen, chest X-ray and/or ventilation study may be abnormal)
Very low probability	• Nonsegmental perfusion defects (e.g., cardiomegaly, enlarged aorta, enlarged hila, elevated diaphragm) • Any perfusion defect with a substantially larger chest X-ray abnormality • Perfusion defects matched by ventilation abnormality provided that there are: (1) clear X-ray and (2) some areas of normal perfusion in the lungs • Any number of small perfusion defects with a normal chest X-ray
Indeterminate or intermediate probability	• One moderate to two large mismatched segmental perfusion defects or the arithmetic equivalent in moderate or large + moderate defects[a] • Single matched ventilation-perfusion defect with clear chest X-ray[b] • Difficult to categorize as low or high, or not described as low or high
High probability	• ≥2 large mismatched segmental perfusion defects or the arithmetic equivalent in moderate or large + moderate defects

Abbreviations: PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis; V/Q, ventilation/perfusion scan.
[a]Two large, mismatched perfusion defects are borderline for "high probability." Individual readers may correctly interpret individual scans with this pattern as "high probability." In general, it is recommended that more than this degree of mismatch be present for the 'high probability" category.
[b]Very extensive matched defects can be categorized as "low probability." Single V/Q matches are borderline for "low probability" and thus should be categorized as "intermediate" in most circumstances by most readers, although individual readers may correctly interpret individual scans with this pattern as "low probability."
Source: Gottschalk et al 1993.[41]

Following PIOPED I and PIOPED II, the prospective multicenter PIOPED III study was conducted between 2006 and 2008 to determine the diagnostic accuracy of the gadolinium-enhanced magnetic resonance angiography (Gd-MRA) of the pulmonary arteries alone and in combination with MRV in patients clinically suspected of having acute PE.[44] To avoid a disproportional number of patients with negative test results, the patients, in whom PE was ruled out using a composite reference test following the methods of PIOPED II study, were randomly sampled for Gd-MRA/MRV.[44,45] The study showed that Gd-MRA combined with MRV yielded a higher sensitivity (92%) and comparable specificity (96%) in patients with technically adequate investigations, compared with Gd-MRA alone (78 and 99% for sensitivity and specificity, respectively). However, the combined approach had a significantly higher proportion of technically inadequate results (52% of 370 patients) as compared with Gd-MRA alone (25% of 371 patients), because it was required that both tests were technically adequate to rule out VTE. Reasons for the high rate of technical inadequacy of MRA were the strict definition for complete vascular opacification and the motion artifact. While MRI brings about many advantages, including its noninvasive nature, safe contrast agents, and (perhaps most importantly) the inherent lack of ionizing radiation, the technique did not prove useful in clinical practice because of susceptibility to artifacts and lack of consistent technical quality among centres and limited MRI availability. To evaluate whether MRI could still be used as a reliable stand-alone test for PE diagnosis, the prospective IRM-EP study was performed between 2008 and 2009.[46] This French, single-center study evaluated the diagnostic accuracy of MRI, using novel magnetic resonance (MR) sequences including unenhanced and contrast-enhanced perfusion sequences in addition to the conventional angiographic MRI sequences (i.e., MRA) for PE diagnosis. Each MR sequence was assessed independently by two readers to assess the level of interobserver agreement. Combining all three MR sequences for patients with technically adequate imaging results, the overall sensitivity ranged from 79 to 90% and the specificity from 99 to 100%, using 64-detector CTPA as the reference standard. If assessed on a vascular level, it was observed that the sensitivity notably decreased with vessel size; the sensitivity ranged from 68 to 92% for segmental PE and from 21 to 33% for subsegmental PE. Considering the MR sequences individually, the contrast-enhanced perfusion sequence and MRA demonstrated the highest sensitivity on these levels. The proportion of technically inadequate results was high (30% of 274 exams) and similar to that of the PIOPED III study. Despite the technical improvements, overall the study demonstrated that MRI cannot be used as a stand-alone test to exclude PE due to its limited sensitivity.

With MRI still insufficient to use as routine test for diagnosing acute PE in clinical practice, CTPA has been the imaging test of choice for more than two decades (►**Fig. 5**).[34,47] CTPA enables the detection of clots in the pulmonary arteries fast and accurate, with a diagnostic accuracy similar to that reported for invasive pulmonary angiography.[47] CTPA studies using the multidetector row technique showed a sensitivity between 96 and 100% and a specificity between 97 and 98%.[38] The 3-month VTE risk in patients with a high clinical probability of PE, who were left



Twenty-nine-year female with acute pulmonary embolism in subsegmental pulmonary arteries.

Fig. 5 Multidetector computed tomography pulmonary angiography images, transverse orientation with view from below, 3.0-mm slice reconstructions. Arrows indicate bilateral acute pulmonary embolism.

untreated because of a negative multidetector CTPA result, has been shown to be low (1.9%; 95% CI, 0.7–20).[48] Furthermore, CTPA offers convenience to the treating physician: CT-based diagnostic algorithms are simpler than V/Q scan-based algorithms and CTPA can be used to diagnose other conditions such as bone fractures, pneumonia, aortic dissection of cancer. CTPA also comes with limitations: patients are subjected to ionizing radiation and the contrast material may cause temporarily increases in the creatinine level as well as allergic reactions.[49,50] Moreover, with advancing CT techniques and higher image quality, increasingly smaller clots can be visualized, up to the subsegmental level: agreement on the presence of these subsegmental pulmonary emboli by expert radiologists is poor and their relevance has been debated.[51–55] Hence, advances in CT techniques may come with overdiagnosis. In parallel with the increasing availability and accuracy of the CTPA, diagnostic algorithms have been designed and validated to rule out PE without performing imaging test, mostly by combining pretest probability (PTP) assessment with a D-dimer blood test.[56–64] Modern algorithms based on PTP-dependent D-dimer thresholds can be used to prevent imaging in over 50% of patients presenting with suspected PE, save costs, and improve efficacy of the diagnostic management at the emergency room, and, importantly, lead to a lower prevalence of subsegmental PE.[57,64–66] Withholding anticoagulant therapy without further testing has been shown to be safe in suspected PE patients, who have a low PTP and a negative D-dimer test.[57] Lastly and importantly, accurate evaluation of CTPA images may reveal important prognostic information, as signs of chronic clot or evolving pulmonary hypertension predict a future diagnosis of chronic thromboembolic pulmonary hypertension.[67–71]

Dual-energy computed tomography (DECT) may provide even more imaging biomarkers to guide PE management than CTPA. DECT involves acquisition of two or more CT measurements with distinct energy spectra. Using the differential attenuation at different X-ray energies, DECT allows distinction of tissues and materials beyond that possible with conventional CT.[72] DECT can be used to acquire perfusion images. This has been shown to improve the diagnostic accuracy of especially subsegmental PE, but its additional benefit for determining patient prognosis is limited. Large prospective diagnostic outcome studies using DECT are currently unavailable.

Single-photon emission computed tomography ventilation/perfusion (SPECT V/Q) imaging may also serve as alternative for CTPA as it involves less ionizing radiation. This scintigraphy technique was primarily developed in response to prevailing concerns about high radiation exposure during CTPA. By using three-dimensional imaging and tomographic imaging, SPECT offers an important technical advantage when compared with conventional planar VQ. This advantage resides in the ability to reduce overlap of perfusion defects caused by other structures and more accurate detection of abnormalities at the subsegmental level and in the lung bases through improved spatial contrast. Accordingly, it was possible to reduce the V/Q scan interpretation categories to a binary outcome, either being affirmative or negative with respect to PE. Large prospective diagnostic outcome studies using SPECT V/Q are currently unavailable.

Derivation and Validation of Clinical Decision Rules to Rule Out Venous Thromboembolism

Noninvasive imaging such as US is not perfectly accurate; therefore, serial testing over a one-week period is recommended to detect DVT in the proximal veins of the lower extremities for those patients who initially test negative on US. In the 1980s, standardized scoring systems (called CDRs or clinical prediction rules) integrating risk factors and clinical signs and symptoms began to emerge to guide the examination of patients suspected of having DVT, in an effort to mitigate the costs and complications of unnecessary testing. The first substantive CDR with potential practical application was derived in 1990 by Landefeld et al based on a retrospective chart review of 354 patients with suspected DVT who underwent venography.[73] In 1995, Wells et al developed the very first Wells score for estimating the PTP of DVT.[74] The original Wells score that incorporated items compiled through literature review and clinical expertise required the assessment of 12 clinical variables (►**Table 3**). After a pilot study, the Wells score was prospectively tested for its ability to reliably stratify 529 symptomatic outpatients with suspected DVT into groups with high, moderate, or low probability of DVT. Only if US results and clinical PTP estimates were discordant, confirmation of DVT was achieved by venography, reducing the number of false-positive and false-negative results. The scoring system

Table 3 The original Wells score for predicting deep vein thrombosis

Major points	Minor points
• Active cancer • Paralysis, paresis, or recent plaster of lower extremities • Recent immobilization >3 d or surgery, within 4 wk • Localized tenderness along the deep vein distribution • Swollen thigh and calf (measured) • Strong family history of deep vein thrombosis	• Recent trauma to symptomatic leg • Pitting edema in symptomatic leg • Dilated superficial (nonvaricose) veins in symptomatic leg • Hospitalization in last 6 mo • Erythema

Source: Wells et al 1995.[74]

Notes: Clinical probability—high: ≥3 major points and no alternative diagnosis, or ≥2 major + ≥2 minor points but no alternative diagnosis; low: 1 major point + ≥2 minor points + an alternative diagnosis, or 1 major point + ≥1 minor points but no alternative diagnosis, or 0 major points + ≥3 minor points + an alternative diagnosis, or 0 major points + ≥2 minor points but no alternative diagnosis; moderate: all other combinations.

Table 4 The revised Wells score for predicting deep vein thrombosis

Variable	Points
Active cancer	1
Paralysis, paresis, or recent plaster of lower extremities	1
Recent immobilization >3 d or surgery, within 4 wk	1
Localized tenderness along the deep vein distribution	1
Entire leg swollen	1
Swollen calf >3-cm difference (measured)	1
Pitting edema	1
Collateral superficial (nonvaricose) veins	1
Alternative diagnosis likely	−2
Clinical probability	
High	≥3
Moderate	1–2
Low	≤0

Source: Wells et al 1997.[75]

was later refined through logistic regression and narrowed down to nine clinical variables, which were related to medical history, aspects of physical examination, and a subjective element of considering an alternative diagnosis (►**Table 4**).[75] In 1997, Wells et al prospectively validated the revised Wells score by examining 593 outpatients with suspected DVT.[75] The CDR showed to be safe and feasible.[75] For patients with a low PTP, the prevalence of DVT was 3%, whereas it was 17 and 75% in patients with moderate or high PTP, respectively. Only three (0.6%) of 501 (95% CI, 0.1–1.8) patients who were initially considered not to have DVT had a VTE event during 3-month follow-up. In a follow-up study conducted in 2003, the score was simplified to two PTP categories instead of three, classifying patients as either likely or unlikely to have DVT.[76] The scoring system was enhanced by incorporating D-dimer testing and a previous diagnosis of DVT. The diagnostic management study demonstrated that patients with a normal D-dimer test result and an unlikely clinical probability of DVT according to the two-level Wells score can safely be withheld from US testing and anticoagulant treatment. The combination of a low PTP and normal D-dimer showed a 3-month VTE failure rate of 0.9% (95% CI, 0.1–3.3). Patients with either high D-dimer but normal US or high PTP, normal US, and normal D-dimer had no recurrent VTE at 3-month follow-up (upper 95% CI, 2.0%).

For suspected PE, the most widely used and externally validated prediction rules are the Wells score and the Geneva score. Using the experience gained from the development of the Wells score for DVT in 1995, Wells and colleagues designed a three-level Wells score in 1998 to classify patients as having a low, intermediate, or high risk of PE.[74,77] This scoring system was originally developed to overcome the low specificity of V/Q scans. In 2000, the score underwent revision using logistic

Table 5 The original and simplified Wells score for predicting pulmonary embolism

Variable	Points	
	Original Wells score	Simplified Wells score
Malignancy	1	1
Hemoptysis	1	1
Heart rate >100 beats/min	1.5	1
Previous DVT or PE	1.5	1
Recent immobilization ≥3 d or surgery within 4 wk	1.5	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Clinical probability		
Two-level		
PE likely	>4	>1
PE unlikely	≤4	≤1
Three-level		
High	>6	–
Moderate	2–6	–
Low	≤1	–

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.
Sources: Wells et al 2000[78]; van Belle et al 2006[79]; Douma et al 2011.[59]

regression and was augmented with D-dimer measurement to enhance diagnostic accuracy.[78] In addition, the score was simplified by categorizing PTP into two risk groups (i.e., PE likely and PE unlikely) to improve clinical applicability and adherence to the CDR (►**Table 5**). Notably, there were no large prospective studies evaluating this dichotomized version of the Wells score until 2006.[79] In that year, the Christopher study was published. This study was conducted to investigate whether a two-level Wells score, classifying patients as either "PE likely" or "PE unlikely," in combination with a D-dimer test is safe to rule out PE in both inpatients and outpatients with a clinical suspicion. Among patients in whom PE was excluded by an unlikely PTP combined with a normal D-dimer (32%), 5 out of 1,028 untreated patients developed VTE during 3-month follow-up (0.5%; 95% CI, 0.2–1.1). The study also aimed to determine the safety of helical CT to rule out PE without further diagnostic tests. A negative CT result safely negated further testing and anticoagulation treatment in most patient; 18 out of 1,446 untreated patients experienced a VTE event during follow-up (1.3%; 95% CI, 0.7–2.0). Finally, Gibson et al introduced the simplified Wells score, which assigns one point to each of the seven variables of the scoring system (►**Table 5**).[80] Its validity and clinical utility were subsequently confirmed in the prospective Prometheus study in 2011, which showed that the simplified score had similar diagnostic performance to its original version using variable weighting.[59]

Table 6 The original Geneva score for predicting pulmonary embolism

Variable	Points
Age: 60–79 y	1
Age: ≥80 y	2
Previous DVT or PE	2
Recent surgery within 4 wk	3
Heart rate: >100 beats/min	1
$PaCO_2$: <35 mm Hg	2
$PaCO_2$: 35–39 mm Hg	1
PaO_2: <49 mm Hg	4
PaO_2: 49–59 mm Hg	3
PaO_2: 60–71 mm Hg	2
PaO_2: 72–82 mm Hg	1
Band atelectasis on chest X-ray	1
Elevation of hemidiaphragm on chest X-ray	1
Clinical probability	
Three-level	
High	>8
Moderate	5–8
Low	<5

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; $PaCO_2$, partial arterial pressure of carbon dioxide; PaO_2, partial arterial pressure of oxygen.
Source: Wicki et al 2001.[81]

Table 7 The revised and simplified Geneva score for predicting pulmonary embolism

Variable	Points	
	Revised Geneva score	Simplified Geneva score
Age: >65 y	1	1
Previous DVT or PE	3	1
Recent surgery or fracture within 4 wk	2	1
Active malignancy	2	1
Unilateral lower limb pain	3	1
Hemoptysis	2	1
Pain on deep vein palpitation of lower limb and unilateral edema	4	1
Heart rate: 75–94 beats/min	3	1
Heart rate: ≥95 beats/min	5	2
Clinical probability		
Two-level		
PE likely	≥6	≥3
PE unlikely	0–5	0–2
Three-level		
High	≥11	≥5
Moderate	4–10	2–4
Low	0–3	0–1

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.
Sources: Le Gal et al 2006[82]; Klok et al 2008.[83]

In 2001, the Geneva score was developed by Wicki et al.[81] The very first version of the Geneva score included nonclinical items, requiring a chest X-ray and an arterial blood gas sample to be taken while breathing room air (►**Table 6**). This hindered its applicability in all patients. In view of this limitation, a modified version including only clinical items was derived and externally validated by Le Gal et al in 2006.[82] This so-called "Revised Geneva score" (RGS) comprised eight variables with different individual weights (►**Table 6**). In 2008, Klok et al published a newer revision referred to as the simplified Geneva score (SGS), giving each item a score of one when present, to prevent miscalculations in acute care due to variable weighting (►**Table 7**).[83] The derivation and validation study of Klok et al showed that the diagnostic accuracy of the simplified version of the RGS did not decrease, showing comparable prevalence of PE in both trichotomized and dichotomized PTP categories compared to the RGS as well as to the original Geneva score, Wells rule, and the rule by Kline et al.[84] Then, in 2017, the SGS underwent external validation in the ADJUST-PE management study, showing equivalent efficiency and safety to the RGS when using the SGS in outpatients with suspected PE.[85] Using the SGS, 608 (38%), 980 (61%), and 33 (2.0%) patients were classified as having a low, intermediate, and high PTP, respectively. Corresponding prevalence of PE were 9.7, 22, and 46%. Among the patients with a low or intermediate PTP, 490 (31%) had a D-dimer level below 500 µg/L (i.e., normal), and 653 (41%) had a D-dimer level within the normal range according to the age-adjusted cutoff. Using the RGS, the figures were 491 (30%) and 650 (40%). During the 3-month follow-up period, none of the patients considered as not having PE based on a low or intermediate PTP (using the RGS or SGS) and a normal D-dimer test experienced a recurrent VTE event.

Since the importance of clinical probability estimation has been emphasized on many occasions, various other CDRs have been developed and validated in different health care settings and specific subgroup of patients.[56–58,86–88] Accordingly, guidelines on the diagnostic management of VTE recommend a diagnostic workup involving assessment of PTP based on validated CDRs, followed by D-dimer measurement in patients with low or intermediate PTP or who are PE unlikely.[24] Notably, two newer CDRs (i.e., the YEARS algorithm and Pulmonary Embolism Graduated D-Dimer [PEGeD] algorithm) use D-dimer cutoffs adjusted to PTP; 1000 ng/mL for low PTP and 500 ng/mL in the case of a high PTP, according to the YEARS algorithm, or moderate PTP, according to the PEGeD algorithm.[57,86]

Conclusion

Imaging techniques to capture VTE have greatly advanced over the last decades. A striving toward more accurate and less

invasive diagnostics has driven the exploration and implementation of CDRs and a variety of imaging technologies, ranging from impedance measurement and US, through X-ray and scintigraphy-based techniques, to MR. Currently, CUS is the preferred diagnostic technique for diagnosing DVT of the legs and CTPA for acute PE. Future technological advances will without a doubt drive further improvements in VTE diagnosis.

Conflict of Interest
None declared.

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